EPA Reviewer: Sheryl K. Reilly, Ph.D. SKR Date: 10-2-95
Biopesticides and Pollution Prevention Division (7501W)

DATA EVALUATION REPORT

STUDY TYPE: Acute Oral Toxicity Rat (152-10)

CASE NO.: 025149

TOX. CHEM. NO: 105401

D.P. BARCODE: D206767

MRID NO.: 433333-01

TEST MATERIAL: Altosid 150 Day Briquet

SYNONYMS: Methoprene, Altosid XR Extended Residual Briquets

STUDY NUMBER: Pharmaco LSR Study Number: 93-0900; Sandoz TDS: DP 301408

SPONSOR: Sandoz Agro, Inc., 1300 E. Touhy Avenue, Des Plaines, IL 60018

TESTING FACILITY: Pharmaco LSR, Inc., Toxicology Services North America, P.O. Box 2360, Mettlers Road, East Millstone, New Jersey 08875-2360

TITLE OF REPORT: Acute Oral Toxicity Study of Altosid 150 Day Briquet in Rats

AUTHOR: Donna L. Blaszcak

REPORT ISSUED: May 3, 1994 (study completion date)

EXECUTIVE SUMMARY: Sprague-Dawley rats (5/sex) were treated with a single oral dose of Altosid 150 Day Briquet at 5100 mg/kg body weight. The test substance was prepared for administration by grinding with a mortar and pestle and mixing with distilled water to provide a 500 mg/mL solution. Rats were treated with the solution of Altosid 150 Day Briquet at a volume of 10.2 mL/kg body weight, and observed for 14 days following dosing.

There were no deaths, and body weights increased for all animals. There were no significant clinical signs during the study, nor significant macroscopic pathological observations at termination.

Under the conditions of this study, **the oral LD_{50} for Altosid 150 Day Briquet is > than 5100 mg/kg body weight for Sprague-Dawley rats.** Altosid 150 Day Briquet is classified in **Toxicity Category IV.** This study is classified as **Acceptable**,

A. MATERIALS

1. Test material: Altosid 150 Day Briquet

Description: gray-black solid with slight hydrocarbon odor
Lot/Batch No.: 310010
Purity: responsibility of the sponsor
Stability of compound: responsibility of the sponsor

2. Test animals

Species: rat
Strain: Sprague-Dawley CD®
Age and weight at study initiation: 9-12 weeks; pretest (day 0) 349-371 g (males), 231-252 g (females)
Source: Charles River Breeding Laboratories, Inc., Kingston, New York 12484

3. Animal care

Housing: individually in suspended stainless steel cages with wire mesh bottoms
Food: Certified Purina Laboratory Chow No. 5002 (PMI Feeds, Inc.), *ad libitum*
Water: municipal water supply, automatic watering system, *ad libitum*
Acclimation period: 14 days
Environmental conditions:
Temperature: 64-76°F
Humidity: 16-52%
Photoperiod: 12 hour light/dark cycle

B. METHODS

After an overnight (18 hour) fast, the test animals (5/sex) were given a single oral gavage dose (5100 mg/kg) administered with a ball-tipped intubation needle fitted to a syringe. The test material was prepared for administration by grinding Altosid 150 Day Briquet with a mortar and pestle, adding distilled water to produce a 500 mg/mL mixture, mixing with a spatula and then with a homogenizer. The test material was prepared just prior to dosing and was mixed well during dosing. The dose volume was 10.2 mL/kg. The individual doses were determined based upon day 0 (prior to fasting) body weights. Animals were observed at 1, 2, and 4 hours after administration of test material and once daily thereafter for 14 days. Animals were examined for general condition, and abnormalities of skin and fur, eyes, nose, oral cavity, abdomen and external genitalia, as well as evaluations of respiration and palpation for tissue masses. Animals were observed twice daily for mortality. Food consumption was not monitored. Body weights were recorded at day 0 (prior to dosing), day 1 (day of dosing), and days 8 and 15 (termination). At termination, all surviving animals were euthanitized by carbon dioxide inhalation and gross necropsies performed. The macroscopic pathological examination included the external surface, all orifices, the organs and tissues of the cranial, thoracic, abdominal, and pelvic cavities, the neck and reminder of the carcass. The LD_{50} was not calculated using a statistical method as there was no mortality.

C. RESULTS

1. Mortality

There were no deaths, and thus the calculated LD_{50} values are greater than 5100 mg/kg for Sprague Dawley rats.

2. Clinical observations

There were no significant toxicological observations.

3. Body weight

There were no treatment-related effects on body weights. Body weights decreased from day 0 to day 1, ranging from 25-32 g for males and from 16-23 g for females. Body weights increased from day 0 to day 8, ranging from 31-45 g for males, and from 4-15 g for females. Body weights increased from day 0 to day 15, ranging from 78-109 g for males, and from 18-40 g for females. Overall group mean body weight gains from day 0 to day 15 were 96.6 g for males, and were 32.2 g for females.

4. Necropsy

There were no significant macroscopic pathological observations.

5. LD_{50}

Under the conditions of this study, the oral LD_{50} for Altosid 150 Day Briquet is greater than 5100 mg/kg body weight for male and female Sprague-Dawley rats. Based upon these LD_{50} values, Altosid 150 Day Briquet is classified in Toxicity Category IV.

D. Signed and dated Quality Assurance and GLP statements were present.

DATA EVALUATION REPORT

ALTOSID 150 DAY BRIQUET

Study Type: ACUTE GAVAGE - RAT (81-1)

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Crystal Station I
2800 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
Health Sciences Research Division
Oak Ridge National Laboratory*
Oak Ridge, TN 37831
Task Order No. 95-1

Primary Reviewer:
C. Scott Jamison, Ph.D.

Signature: C S Jamison
Date: 8/14/95

Secondary Reviewers:
Cheryl B. Bast, Ph.D., D.A.B.T.

Signature: C B Bast
Date: 8-15-95

Robert H. Ross, M.S., Group Leader

Signature: Robert H Ross
Date: 8/28/95

Quality Assurance:
Susan Chang, M.S.

Signature: S S Chang
Date: 8/24/95

Disclaimer

The final Data Evaluation Report may have been altered by the Health Effects Division subsequent to signing by Oak Ridge National Laboratory personnel.

*Managed by Lockheed Martin Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400

DATA EVALUATION REPORT

ALTOSID 150 DAY BRIQUET

Study Type: ACUTE DERMAL - RABBIT (81-2)

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Crystal Station 1
2800 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
Health Sciences Research Division
Oak Ridge National Laboratory*
Oak Ridge, TN 37831
Task Order No. 95-1

Primary Reviewer:
C. Scott Jamison, Ph.D.

Signature: C. Scott Jamison
Date: 8/24/95

Secondary Reviewers:
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Signature: CBBast
Date: 8-25-95

Robert H. Ross, M.S., Group Leader

Signature: Robert H. Ross
Date: 8/28/95

Quality Assurance:
Susan Chang, M.S.

Signature: Susan Chang
Date: 8/24/95

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EPA Reviewer: Sheryl K. Reilly, Ph.D. SKR Date: 10-2-95
Biopesticides and Pollution Prevention Division (7501W)

DATA EVALUATION REPORT

STUDY TYPE: Acute Dermal - Rabbit (152-11)

CASE NO.: 025149

TOX. CHEM. NO: 105401

DP BARCODE.: D206767

MRID NO.: 433333-02

TEST MATERIAL: Altosid 150 Day Briquet

SYNONYMS: Methoprene, Altosid XR Extended Residual Briquet

STUDY NUMBER: Pharmaco LSR Study No.: 93-0901; Sandoz TDS Study No.: DP 301409

SPONSOR: Sandoz Agro, Inc., 1300 E. Touhy Avenue, Des Plaines, IL 60018

TESTING FACILITY: Pharmaco LSR, Inc., Toxicology Services North America, P.O. Box 2360, Mettlers road, East Millstone, New Jersey 08875-2360

TITLE OF REPORT: Acute Dermal Toxicity Study of Altosid 150 Day Briquet in Rabbits

AUTHOR: Donna L. Blaszcak

REPORT ISSUED: May 3, 1994 (study completion date)

EXECUTIVE SUMMARY: Hra:(NZW)SPF rabbits (5/sex) were treated with a single dermal dose of Altosid 150 Day Briquet at 2100 mg/kg body weight for 24 hours and observed for 14 days following treatment. For treatment, Altosid 150 Day Briquet was ground with a mortar and pestle, added to gauze, and moistened with saline.

There was no mortality, no severe dermal irritation, no adverse clinical signs, no adverse effects on body weight gain, and no macroscopic pathological findings for male or female rabbits treated with Altosid 150 Day Briquet.

Under the conditions of this study, **the dermal LD_{50} for Altosid 150 Day Briquet is > 2100 mg/kg body weight for New Zealand White rabbits.** Based upon the study results, Altosid 150 Day Briquet is classified in **Toxicity Category III**. This study is **Acceptable**.

A. MATERIALS

1. Test material: Altosid 150 Day Briquet

Description: gray-black solid with hydrocarbon odor
Lot/Batch No.: 310010
Purity: responsibility of the sponsor
Stability of compound: responsibility of the sponsor
Active ingredient: not reported

2. Test animals

Species: rabbit
Strain: Hra:(NZW)SPF
Age and weight at study initiation: ≥8 weeks; pretest (day 0): 2.1-2.3 kg (males), 2.3-2.5 kg (females)
Source: HRP, Inc., Denver, PA

3. Animal care

Housing: individually in suspended stainless steel cages with wire mesh bottoms
Food: Lab Rabbit Chow HF (Purina #5326)
Water: municipal water supply, automatic watering system, *ad libitum*
Acclimation period: 24 days
Environmental conditions:
Temperature: 64-70°F
Humidity: 22-56%
Photoperiod: 12 hour light/dark cycle

B. METHODS

The hair on the trunk (dorsal surface and sides from the scapula to the pelvic area) of 10 NZW rabbits (5/sex) was clipped with electric clippers 24 hours prior to dosing. At least 10% of the total body surface on each animal (12 cm x 14 cm) was exposed and no abrasions were noted. The test substance was prepared for administration by grinding with a mortar and pestle, then placed onto a strip of 8-ply gauze and moistened with ~1 mL of saline. The gauze was wrapped around the trunk of the animal, covering the application site. An impervious plastic sleeve was wrapped over the gauze and secured with Elastoplast® tape, in order to contain the test material without leakage or undue pressure. Elizabethan collars were placed onto all animals in order to prevent ingestion of the test material or disruption of the wrappings. The bandaging was removed after 24 hours, and the test site wiped free of excess test material with distilled water and gauze. Animals were observed for signs of toxicity at 1, 2, and 4 hours after test material application and daily thereafter for 14 days. Animals were examined for severe dermal effects, general condition, and for abnormalities of skin and fur, eyes, nose, oral cavity, abdomen and external genitalia as well as evaluations of respiration and palpation for tissue masses. Mortality observations were performed twice daily. Body weights were determined at days 0 (prior to clipping), 1 (prior to dosing), 8, and 15 (termination). Day 0 body weights were used

to calculate the doses. All animals were euthanitized on day 15 by an intravenous overdose of sodium pentobarbital and subjected to gross pathological examination of the external surface, all orifices, the organs and tissues of the cranial, thoracic, abdominal and pelvic cavities and neck and the remainder of the carcass. Food consumption data were not reported. The dermal exposures to Altosid 150 Day Briquet at 2100 mg/kg corresponded to ~29 mg/cm^2 for males and ~28 mg/cm^2 for females (calculated by the reviewer).

C. RESULTS

1. Mortality

There was no mortality during the 14 day observation period.

2. Clinical observations

There were no treatment-related clinical signs.

3. Body weight

Body weight gains over the 14 day observation period were 0.0, 0.1, 0.0, -0.1, and 0.0 kg for males and were -0.1, 0.0, 0.0, -0.1, and 0.0 kg for females.

4. Necropsy

There were no gross pathological findings for male or female rabbits.

5. LD_{50}

The LD_{50} was not calculated using a statistical analysis, as there was no mortality. The dermal LD_{50} for Altosid 150 Day Briquet is greater than 2100 mg/kg body weight for New Zealand White rabbits.

D. Signed and dated Quality Assurance and GLP statements were present.

DATA EVALUATION REPORT

ALTOSID 150 DAY BRIQUET

Study Type: ACUTE DERMAL - RABBIT (81-2)

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Crystal Station I
2800 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
Health Sciences Research Division
Oak Ridge National Laboratory*
Oak Ridge, TN 37831
Task Order No. 95-1

Primary Reviewer:
C. Scott Jamison, Ph.D.
Signature: C. S. Jamison
Date: 8/24/95

Secondary Reviewers:
Cheryl B. Bast, Ph.D., D.A.B.T.
Signature: C B Bast
Date: 8-25-95

Robert H. Ross, M.S., Group Leader
Signature: Robert H. Ross
Date: 8/28/95

Quality Assurance:
Susan Chang, M.S.
Signature: Susan Chang
Date: 8/24/95

Disclaimer

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*Managed by Lockheed Martin Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400

EPA Reviewer: Sheryl K. Reilly, Ph.D. SKR Date: 10-2-95
Biopesticides and Pollution Prevention Division (7501W)

DATA EVALUATION REPORT

STUDY TYPE: Primary Eye Irritation-Rabbit (152-13)

CASE NO.: 025149

TOX. CHEM. NO: 105401

DP BARCODE.: D206767

MRID NO.: 433333-03

TEST MATERIAL: Altosid 150 Day Briquet

SYNONYMS: Methoprene, Altosid XR Extended Residual Briquet

STUDY NUMBER: Pharmaco LSR Study No.: 93-0903; Sandoz TDS Study No.: DP 301411

SPONSOR: Sandoz Agro, Inc., 1300 E. Touhy Avenue, Des Plaines, IL 60018

TESTING FACILITY: Pharmaco LSR, Inc., Toxicology Services North America, P.O. Box 2360, Mettlers road, East Millstone, New Jersey 08875-2360

TITLE OF REPORT: Primary Eye Irritation Study of Altosid 150 Day Briquet in Rabbits

AUTHOR: Donna L. Blaszcak

REPORT ISSUED: May 3, 1994 (study completion date)

EXECUTIVE SUMMARY: Hra:(NZW)SPF rabbits (5 males, 4 females) were treated with a single ocular dose (0.1 cm^3) of ground, dry Altosid 150 Day Briquet. The test material was administered into the lower conjunctival sac of the right eye of each animal and the eye held shut for 1 second. The eyes of 3 rabbits (2 males, 1 female) were washed with water 20-30 seconds after dosing. The treated eye of 1 female rabbit (unwashed eye group) was washed 24 hours after dosing to remove remaining residual test material. The contralateral eye of each rabbit served as a control. The eyes of all rabbits were checked for irritation at 1, 24, 48, and 72 hours, and 6 days after dosing or until irritation cleared.

For the rabbits treated with Altosid 150 Day Briquet without eye washing, eye irritation consisted of slight to mild conjunctival irritation in 6/6 rabbits and iritis in 4/6 rabbits at 1 hour post-treatment. Conjunctivitis persisted in 5/6 rabbits through 48 hours post-treatment. Corneal opacity was evident in 1 rabbit at 24 hours. Corneal ulceration was evident in 3/6 rabbits at 24 hours and in 1 rabbit at 48 hours. At 72 hours post-treatment, eye irritation had cleared in 5/6 rabbits. Slight redness of the conjunctivae was apparent in 1 male at 72

hours and cleared at 6 days post-treatment. In the unwashed eye group, eye irritation consisted of slight to mild conjunctivitis in 3/3 rabbits at 1 hour, and slight redness of the conjunctivae in 2/3 rabbits at 24 hours post-treatment. For rabbits in the washed eyes group, ocular irritation cleared by 48 hours.

As there was corneal involvement and conjunctivitis present at 24 hours post-treatment, but clearing within 7 days, **Altosid 150 Day Briquet is classified as a mild irritant** to the eyes of male and female New Zealand White rabbits and is placed in **Toxicity Category III.** This study is **Acceptable**.

A. MATERIALS

1. Test material: Altosid 150 Day Briquet

   Description: gray/black solid with slight hydrocarbon odor
   Lot/Batch No.: 310010
   Purity: responsibility of the sponsor
   Stability of compound: responsibility of the sponsor
   Active ingredient: not reported
   *p*H: not reported

2. Test animals

   Species: rabbit
   Strain: New Zealand white, Hra:(NZW)SPF
   Age and weight at study initiation: ≥8 weeks; 1.9-2.3 kg
   Source: HRP, Inc., Denver, PA

3. Animal care

   Housing: individually in suspended stainless steel cages with wire mesh bottoms
   Food: Lab Rabbit Chow HF (Purina #5326)
   Water: municipal water supply, automatic watering system, *ad libitum*
   Acclimation period: 8 days
   Environmental conditions:
   Temperature: 64-70°F
   Humidity: 18-42%
   Photoperiod: 12 hour light/dark cycle

B. METHODS

Altosid 150 Day Briquet was ground with a mortar and pestle prior to administration. Nine rabbits (5 males, 4 females) were treated with a single dose ocular (0.1 cm^3) of the test material. Both eyes of each animal were examined on the day before dosing (using fluorescein dye) and on the day of dosing (without dye) to check for the presence of corneal ulceration. Only animals negative for corneal ulceration, conjunctival injury, or irritation were used in the study. The test material was introduced into the lower conjunctival sac of the right eye of each animal and the eyelids held shut for 1 second to prevent loss of

material. The untreated eye served as a control. After 20-30 seconds, the eyes of 3 rabbits (2 males, 1 female) were washed for approximately 1 minute with lukewarm water. The eyes of the remaining six rabbits (3 males, 3 females) were left unwashed. After 24 hours, there was no residual test material present in the treated eye of 5/6 rabbits in the unwashed eye group. The treated eye of 1 female in the unwashed eye group was rinsed 24 hours after dosing in order to remove residual test material. The eyes of all animals were examined at approximately 1, 24, 48, and 72 hours and 6 days after treatment. Fluorescein dye was used to confirm the presence or absence of corneal ulceration, starting at the 24 hour examination. Eye examinations with fluorescein dye continued until there was no dye retention for 2 observations. Any abnormal pharmacological or toxicological signs were noted. Observations for mortality were performed twice daily. There were no body weight changes reported by the study authors. At the termination of the study, all rabbits were euthanitized with sodium pentobarbital. There was no macroscopic examination of tissues.

At each timepoint, the treated eyes were examined and scored for ocular reactions in comparison to the untreated eyes. Ocular reactions were scored for the conjunctivae (redness, chemosis, discharge, and white tissue or ulceration), the iris, and the cornea (opacity, area of corneal involvement, stippling, and ulceration). Irritation was defined as the production of reversible changes. Eye corrosion was defined as the production of irreversible tissue damage to the eye following test material administration. Unusual effects such as pannus, blistering of the conjunctivae, ulceration and other corrosive effects were noted when present.

C. RESULTS

1. Mortality

There was no mortality.

2. Clinical observations

The incidence of eye irritation for males and females is presented in Table 1. Eye irritation for the rabbits treated with Altosid 150 Day Briquet without subsequent eye washing, consisted of mild to moderate conjunctival irritation (redness, chemosis, and/or discharge) at 1, 24, and 48 hours post-treatment, iritis (4/6) at 1 hour post-treatment, corneal opacity at 24 hours (1/6) and corneal ulceration at 24 (3/6) and 48 (1/6) hours post-treatment. At 72 hours post-treatment, there was no eye irritation in 5/6 rabbits. The slight conjunctival redness noted for 1 male at 72 hours cleared by 6 days post-treatment.

For the washed eye group, eye irritation consisted of slight (1 male, 1 female) and mild (1 male) redness of the conjunctivae and slight chemosis (1 male) at 1 hour and slight redness of the conjunctivae (1 male, 1 female) at 24 hours post-treatment. Eye irritation in the washed eyes group cleared by 48 hours post-treatment. There was residual test material present in the eyes of the rabbits in the washed eye group at 1 hour post-treatment, indicating that the 1 minute wash after administration of the test material was insufficient to remove the material from the eye. However, the severity of the irritation was reduced by the washing procedure.

Average ocular irritation scores at each timepoint were calculated from the data by the reviewer (see Table 1, below). The maximum mean irritation score (7.0) was obtained for rabbits in the unwashed eyes group at 24 hours post-treatment. As there were signs of irritation for males and females at 24 and 48 hours post-treatment, and there was slight corneal involvement, Altosid 150 Day Briquet is classified as a mild eye irritant and is in Toxicity Category III for male and female New Zealand white rabbits.

D. Signed and dated Quality Assurance and GLP statements were present.

TABLE 1. INCIDENCE OF OCULAR IRRITATION IN MALE AND FEMALE NEW ZEALAND WHITE RABBITS TREATED WITH ALTOSID 150 DAY BRIQUET

Time Post-Treatment	Cornea		Iritis	Conjunctivae			Mean Score
	Opacity	Ulceration		Redness	Chemosis	Discharge	
Unwashed Eyes							
1 Hour	0/6	0/6	4/6	6/6	5/6	4/6	6.3
24 Hour	1/6	3/6	0/6	6/6	4/6	1/6	7.0
48 Hour	0/6	1/6	0/6	5/6	1/6	0/6	2.3
72 Hour	0/6	0/6	0/6	1/6	0/6	0/6	0.3
Day 6	0/1	0/1	0/1	0/1	0/1	0/1	0.0
Washed Eyes							
1 Hour	0/3	0/3	0/3	3/3	1/3	0/3	1.7
24 Hour	0/3	0/3	0/3	2/3	0/3	0/3	0.7
48 Hour	0/3	0/3	0/3	0/3	0/3	0/3	0.0
72 Hour	0/3	0/3	0/3	0/3	0/3	0/3	0.0

Data adapted from Tables I, II, and III, pp. 19-24, MRID No. 433333-03.

DATA EVALUATION REPORT

ALTOSID 150 DAY BRIQUET

Study Type: PRIMARY EYE IRRITATION - RABBIT (81-4)

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Crystal Station I
2800 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
Health Sciences Research Division
Oak Ridge National Laboratory*
Oak Ridge, TN 37831
Task Order No. 95-1

Primary Reviewer:
C. Scott Jamison, Ph.D. Signature: _____
Date: 8/24/95

Secondary Reviewers:
Cheryl B. Bast, Ph.D., D.A.B.T. Signature: _____
Date: 8-25-95

Robert H. Ross, M.S., Group Leader Signature: _____
Date: 8/28/95

Quality Assurance:
Susan Chang, M.S. Signature: _____
Date: 8/24/95

Disclaimer

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*Managed by Lockheed Martin Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400

EPA Reviewer: Sheryl K. Reilly, Ph.D. SKR Date: 10-2-95
Biopesticides and Pollution Prevention Division (7501W)

DATA EVALUATION REPORT

STUDY TYPE: Primary Skin Irritation - Rabbit (152-14)

CASE NO. 025149

TOX. CHEM. NO: 105401

DP BARCODE.: D206767

MRID NO.: 433333-04

TEST MATERIAL: Altosid 150 Day Briquet

SYNONYMS: Methoprene, Altosid XR Extended Residual Briquet

STUDY NUMBER: Pharmaco LSR Study No.: 93-0902; Sandoz TDS Study No.: DP 301410

SPONSOR: Sandoz Agro, Inc., 1300 E. Touhy Avenue, Des Plaines, IL 60018

TESTING FACILITY: Pharmaco LSR, Inc., Toxicology Services North America, P.O. Box 2360, Mettlers road, East Millstone, New Jersey 08875-2360

TITLE OF REPORT: Primary Dermal Irritation Study of Altosid 150 Day Briquet in Rabbits

AUTHOR: Donna L. Blaszcak

REPORT ISSUED: May 3, 1994 (study completion date)

EXECUTIVE SUMMARY: Hra:(NZW)SPF rabbits (3/sex) were treated with a single dermal dose (0.5 g) of Altosid 150 Day Briquet. The test material was ground to a powder, moistened with saline, applied to the shaved backs of the rabbits, covered with a patch, and was removed by wiping 4 hours later. Rabbits were observed at 0.5, 24, 48, and 72 hours, and 7 days after patch removal.

Very slight erythema was noted in 6/6 rabbits at 0.5 hours after removal of wrappings, in 1/3 males and 2/3 females at 24 hours, in 1/3 males and 1/3 females at 48 hours. There was no erythema noted for any of the rabbits 72 hours after removal of the wrappings. There was no edema or other dermal irritation noted for any of the rabbits at any timepoint. The primary irritation index was 0.45. There were no clinical signs of toxicity.

Based on the results of this study, **Altosid 150 Day Briquet is classified as a mild irritant** to the skin of male and female New Zealand white rabbits and is placed in **Toxicity Category IV.** This study is **Acceptable**.

A. MATERIALS

1. Test material: Altosid 150 Day Briquet

Description: gray-black solid with slight hydrocarbon odor
Lot/Batch No.: 310010
Purity: responsibility of the sponsor
Stability of compound: responsibility of the sponsor
Active ingredient: not reported
*p*H: not reported

2. Test animals

Species: rabbit
Strain: New Zealand white, Hra:(NZW)SPF
Age and weight at study initiation: ≥8 weeks; 2.3-2.4 kg
Source: HRP, Inc., Denver, PA

3. Animal care

Housing: individually in suspended stainless steel cages with wire mesh bottoms
Food: Lab Rabbit Chow HF (Purina #5326)
Water: municipal water supply, automatic watering system, *ad libitum*
Acclimation period: 22 days
Environmental conditions:
Temperature: 64-70°F
Humidity: 34-56%
Photoperiod: 12 hour light/dark cycle

B. METHODS

Six rabbits (3./sex) were treated for 4 hours with a single dermal dose (0.5 g) of Altosid 150 Day Briquet. Approximately 24 hours prior to application, the hair of each animal was clipped with an electric clipper to expose the back from the scapular to the lumbar region, and the skin was examined for abrasions (none were noted in any of the rabbits). The test material was ground with a mortar and pestle, and 0.5 g moistened with 0.5 mL of saline and applied directly to the backs of the rabbits. The test site was covered with gauze (1 inch x 1 inch, approximately 6 cm^2), held in place with tape. Gauze was then wrapped around each animal to hold the test material in place without undue pressure (semi-occlusive pressure). Elizabethan collars were used to restrain the animals during dosing to prevent disruption of the wrappings and ingestion of the test material. After 4 hours of treatment, wrappings were removed and the test site gently wiped free of excess material with gauze and distilled water. Dermal observations were made approximately 0.5, 24, 48, and 72 hours after removal of wrappings. The test site was examined for the presence of erythema, edema, or other evidence of dermal irritation (such as necrosis, eschar, other irreversible alteration of tissue structures, or other dermal abnormalities). Adjacent areas of untreated skin were used as controls. Any abnormal clincal signs of toxicity were noted. Mortality

checks were performed twice daily. At study termination, all rabbits were euthanitized with sodium pentobarbital. There was no gross necropsy performed, and no tissues were saved.

C. RESULTS

The animals all exhibited very slight (barely perceptible) erythema at 0.5 hours after removal of wrappings. At 24 hours, 1/3 males and 2/3 females had very slight erythema. At 48 hours, 1/3 males and 1/3 females were observed with very slight erythema. All signs of dermal irritation cleared by 72 hours after removal of the wrappings. Dermal irritation scores at each timepoint are presented in Table 1. There was no edema or other dermal irritation noted for any of the rabbits at any timepoint.

Other than very slight skin irritation, there were no clinical signs of toxicity noted. Body weight changes, if any, were not reported. There was no mortality.

Altosid 150 Day Briquet is classified as a mild skin irritant, based upon the primary irritation index of 0.45 (the average of the scores obtained from 0.5 through 72 hours post-treatment). At 72 hours post-treatment, there was no skin irritation observable in males or females, thus, Altosid 150 Day Briquet is in Toxicity Category IV.

D. Signed and dated Quality Assurance and GLP statements were present.

TABLE 1. DERMAL IRRITATION SCORES OF MALE AND FEMALE NEW ZEALAND WHITE RABBITS TREATED DERMALLY WITH ALTOSID 150 DAY BRIQUET

Rabbit No./Sex	Time after patch removal			
	0.5 hours	24 hours	48 hours	72 hours
2010/F	1/0[a]	1/0	1/0	0/0
2012/F	1/0	0/0	0/0	0/0
2014/F	1/0	1/0	0/0	0/0
2011/M	1/0	0/0	0/0	0/0
2013/M	1/0	0/0	0/0	0/0
2015/M	1/0	1/0	1/0	0/0
Total[b]	6/0	3/0	2/0	0/0
Average[b]	1/0	0.5/0	0.3/0	0/0

Data adapted from page 17, MRID No. 433333-04.
[a]Erythema/Edema scores (scale from 0 to 4). A 0 indicates no erythema, no edema. A 1 indicates very slight (barely perceptible) erythema.
[b]Calculated by the reviewer.

DATA EVALUATION REPORT

ALTOSID 150 DAY BRIQUET

Study Type: PRIMARY SKIN IRRITATION - RABBIT (81-5)

Prepared for

Biopesticides and Pollution Prevention Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Crystal Station I
2800 Jefferson Davis Highway
Arlington, VA 22202

Prepared by

Chemical Hazard Evaluation Group
Biomedical and Environmental Information Analysis Section
Health Sciences Research Division
Oak Ridge National Laboratory*
Oak Ridge, TN 37831
Task Order No. 95-1

Primary Reviewer:
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Date: 8/24/95

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Date: 8-25-95

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Date: 8/28/95

Quality Assurance:
Susan Chang, M.S.
Signature: Susan Chang
Date: 8/24/95

Disclaimer

The final Data Evaluation Report may have been altered by the Health Effects Division subsequent to signing by Oak Ridge National Laboratory personnel.

*Managed by Lockheed Martin Energy Systems, Inc., for the U.S. Department of Energy under Contract No. DE-AC05-84OR21400

EPA Reviewer: Sheryl K. Reilly, Ph.D. SKR Date: 10-2-95
Biopesticides and Pollution Prevention Division (7501W)

DATA EVALUATION REPORT

STUDY TYPE: Dermal Sensitization, Buehler Method-Guinea Pig (152--15)

CASE NO.: 025149

TOX. CHEM. NO: 105401

DP BARCODE.: D206767

MRID NO.: 433333-05

TEST MATERIAL: Altosid 150 Day Briquet

SYNONYMS: Methoprene, Altosid XR Extended Residual Briquet

STUDY NUMBER: Pharmaco LSR Study No.: 93-0904; Sandoz TDS Study No.: DP 301412

SPONSOR: Sandoz Agro, Inc., 1300 E. Touhy Avenue, Des Plaines, IL 60018

TESTING FACILITY: Pharmaco LSR, Inc., Toxicology Services North America, P.O. Box 2360, Mettlers road, East Millstone, New Jersey 08875-2360

TITLE OF REPORT: Closed Patch Repeated Insult Dermal Sensitization Study of Altosid 150 Day Briquet in Guinea Pigs

AUTHOR: Donna L. Blaszcak

REPORT ISSUED: May 3, 1994 (study completion date)

EXECUTIVE SUMMARY: Dunkin Hartley albino (Haz:(DH)fBR) guinea pigs (10/sex) were treated with 0.3 cm^3 (moistened with 0.3 mL saline) Altosid 150 Day Briquet for 6 hours, once per week for 3 weeks. Two weeks after the last induction exposure, the guinea pigs were challenged with test material applied to a naive site. In order to distinguish an irritation reaction from sensitization, an irritation control group of 5 male and 5 female guinea pigs were subjected to the same challenge procedures, but without the induction regimen. A positive control group (5 males, 5 females) was subjected to 3 inductions with 0.3 mL of 0.005 g/mL (in ethanol) DNCB and challenged with 0.3 mL of 0.003 g/mL (in acetone) DNCB. An irritation control for DNCB was treated with a challenge dose only.

Guinea pigs treated dermally with DNCB all exhibited appropriate skin irritation reactions after the first induction dose, and after challenge. Dermal responses to Altosid 150 Day Briquet after the first induction dose were limited to very slight erythema (1/10 males) at 24 hours, and no dermal responses in 19/20 and 20/20 guinea pigs at 24 and 48 hours,

respectively. There were no dermal responses after challenge with Altosid 150 Day Briquet in 20/20 guinea pigs at 24 or 48 hours post-treatment. The sensitization incidence index to Altosid 150 Day Briquet at 24 hours was 0% for the challenge and irritation control groups. There was no mortality and no treatment-related effects on body weight gain for males or females. There were no clinical signs of toxicity reported.

Based on the results of this study, **Altosid 150 Day Briquet is not a contact sensitizer** in Dunkin Hartley guinea pigs. This study is **Acceptable**.

A. MATERIALS

1. Test material: Altosid 150 Day Briquet

Description: gray-black solid with slight hydrocarbon odor
Lot/Batch No.: 310010
Purity: responsibility of the sponsor
Stability of compound: responsibility of the sponsor
Active ingredient: not reported
*p*H: not reported
Density: not reported

2. Test animals

Species: guinea pigs
Strain: Dunkin Hartley albino; Haz:(DH)fBR
Age and weight at study initiation: 5-6 weeks; 323-460g (males), 261-424 g (females)
Source: HRP, Inc., Denver, PA

3. Animal care

Housing: individually in suspended stainless steel cages with wire mesh bottoms
Food: Agway Prolab Guinea Pig Diet, *ad libitum*
Water: municipal water supply, automatic watering system, *ad libitum*
Acclimation period: 16 days

Environmental conditions:
Temperature: 60-76°F
Humidity: 12-80%
Photoperiod: 12 hour light/dark cycle

B. METHODS

1. Mortality, clinical signs, and body weights

Mortality checks were performed twice daily. Checks for general health were performed prior to treatment and once weekly and any abnormalities noted. Body weights were determined on the day prior to the first induction and at termination (2 days after challenge). Dermal responses were scored for erythema (scale: 0, no reaction; 0.5, very slight; 1, slight; 2, moderate; 3, severe), edema, necrosis, and eschar.

2. Preliminary irritation study

An initial screening was performed in order to determine the irritancy of the test material. The hair was clipped short on the back and sides the guinea pigs on the day prior to the application of the test material. Altosid 150 Day Briquet was applied topically to 6 guinea pigs at 100% (0.3 cm^3 in 0.3 mL saline), 50%, 25%, and 10% concentrations (w/v, diluted into distilled water). The test material mixtures were applied to each guinea pig beneath a Hilltop Chamber® in a volume of 0.3 mL. The chamber was occluded with overlapping, impermeable plastic and secured with an elastic adhesive bandage (Elastoplast®) wound around the torsos of the guinea pigs. The chambers were left in place for 6 hours, then removed and the skin wiped free of excess material with distilled water and gauze. Skin irritation observations were made at 24 and 48 hours.

3. Induction

The hair on the application site (back and sides) of was clipped short with an electric clipper 24 hours prior to each application. A Hilltop Chamber® was saturated with test material (0.3 cm^3 of Altosid 150 Day Briquet) or 0.3 mL of DNCB. The test site was on the right side of the midline. The chamber was covered by overlapping impermeable plastic, held in place with Elastoplast® adhesive elastic bandage wound around the torso of the guinea pig. The chamber was left in place for 6 hours, then removed and the skin wiped free of excess material with distilled water and gauze. Induction was performed once a week, for 3 weeks. Twenty guinea pigs (10/sex) were used for testing dermal sensitization of Altosid 150 Day Briquet; ten animals (5/sex) were used in the positive control group (DNCB). Altosid 150 Day Briquet was ground with a mortar and pestle and 0.3 cm^3 moistened with 0.3 mL of saline. DNCB was dissolved in 80% ethanol to produce a 0.005 g/mL solution that was used for application during induction. Dermal evaluations were made at 24 and 48 hours after the first induction exposure to confirm that a slightly irritating concentration of DNCB was used, and that an appropriate concentration of Altosid 150 Day Briquet had been chosen.

4. Challenge

Fourteen days after the last induction exposure, the test material was administered at a site on the opposite side of the midline from the induction exposure test site. The method for the challenge exposure was the same as was used during the induction exposures, except that the dose of the positive control, DNCB, was lower (0.3 mL of 0.003 g/mL), and the solution used for dissolving DNCB was acetone, rather than ethanol. The dermal response was evaluated 24 and 48 hours after challenge treatment. The results were evaluated by the amount of erythema at the challenge site relative to irritation controls. Two indices were calculated to assess the dermal responses: incidence and severity. The incidence index is the number of animals with a response grade of ≥ 1 (at 24 or 48 hours) out of the total number of animals in the group. The severity index for the 24 and 48 hour response reading was determined by dividing the sum total grades in a group by the total number of animals exposed. At study termination, all guinea pigs were euthanitized with carbon dioxide. There was no gross necropsy performed.

C. RESULTS

1. Mortality, clinical signs, and body weights

There was no mortality, and the animals were in good general health at each of the weekly observations. Body weight gains for guinea pigs treated with Altosid 150 Day Briquet ranged from 165-273 g for males, and from 103-211 g for females. These ranges of body weight gains were similar to those for the positive (156-206 g for males, 135-183 g for females) and the negative/irritation controls (151-250 g for males, 103-248 g for females).

2. Preliminary irritation study

The preliminary skin irritancy test results indicated that Altosid 150 Day Briquet was non-irritating to guinea pigs. There were no erythema, or other skin irritation reactions observed at either the 24 or 48 hour timepoints. There were no other clinical signs of toxicity reported. As a result, Altosid 150 Day Briquet was used undiluted in the induction and challenge portions of the dermal sensitization test.

3. Induction

At the first induction, all 10 guinea pigs treated with DNCB exhibited appropriate dermal responses. At the first induction for guinea pigs treated with Altosid 150 Day Briquet, dermal responses consisted of very slight erythema in only 1/10 males at 24 hours. Dermal responses for DNCB or for Altosid 150 Day Briquet were only recorded by the study authors for the first induction exposure.

4. Challenge

At challenge, the positive (DNCB) control animals exhibited appropriate dermal responses. There was no response at either 24 or 48 hours after challenge in the guinea pigs treated with the test material. The Incidence Index of Sensitization to Altosid 150 Day Briquet at 24 hours was 0%. The Severity Indices at 24 and 48 hours were 0.0 and 0.0, respectively. For irritation controls treated with Altosid 150 Day Briquet, there was no erythema or other dermal response. The Incidence Index of Sensitization at 24 hours was 0% for the irritation control group. The Severity Indices for the irritation control group were 0.0 and 0.0, at 24 and 48 hours, respectively.

Based on the results of this study, Altosid 150 Day Briquet is not a contact sensitizer to the skin of Dunkin Hartley guinea pigs.

D. Signed and dated Quality Assurance and GLP statements were present.

13544

R136065

Chemical: Methoprene

PC Code:
105401

HED File Code: 41500 BPPD Tox/Chem
Memo Date: 10/11/1995
File ID: DPD206767
Accession #: 000-00-9001

HED Records Reference Center
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